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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES





APPEAL BRIEF FOR THE APPELLANT

Michael NAESBY

SMALL TRIPLEX FORMING PNA OLIGOS

Serial No. 09/137,822
Filed: August 21, 1998
Appeal No.:
Group Art Unit: 1655

Enclosed is a check in the amount of Three Hundred Dollars ($310.00) to cover the official fee for this Appeal Brief. In the event that there may be any fees due with respect to the filing of this paper, please charge Deposit Account No. 01-2300.

Respectfully submitted,
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Appeal Brief (in triplicate)

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In re the application of:

Michael NAESBY

Serial Number: 09/137,822

Filed: August 21, 1998

For: SMALL TRIPLEX FORMING PNA OLIGOS


Appeal No.

Examiner: Enewold, J.

Group Art Unit: 1655

**BRIEF ON APPEAL**

November 8, 2000

INTRODUCTION

This is an appeal from the action of the Examiner dated March 10, 2000, finally rejecting claims 31-85, all of the claims pending in this application, as containing new matter and being indefinite under 35 U.S.C. § 112 and being unpatentable over a single reference under 35 U.S.C. § 102(b). A Notice of Appeal was timely filed on September 8, 2000. This Brief is being timely filed.

1. REAL PARTY IN INTEREST

The application has been assigned to Dako A/S, Produktionsvej 42, DK-2600, Glostrup, Denmark. Dako A/S and its affiliated company Boston Probes Inc., 75E Wiggins Ave, Bedford, MA, share an interest in the outcome of this appeal.

## 2. STATEMENT OF RELATED APPEALS AND INTERFERENCES

No related appeals and/or interferences are pending.

## 3. STATUS OF CLAIMS

Claims 31-85, all of the claims pending in the present application, are being appealed. Claims 1-30 have been canceled.

## 4. STATUS OF AMENDMENTS

There are no outstanding amendments to the claims.

The amendment to add new claims 86-137 included with the Response Under 37 C.F.R. 1.116 filed June 28, 2000 has not been entered.

## 5. SUMMARY OF THE INVENTION

The present invention relates to methods for determining nucleic acids via the formation of triple stranded binding complexes as well as such triple stranded binding complexes themselves. In one embodiment, the invention is directed to methods (claims 31-54 and 82-85) for determining a nucleic acid A (see page 5 of the specification, first two full paragraphs, for the description of the nucleic acid analyte, i.e. nucleic acid A, that is to be determined) through the formation of triple stranded complexes of the nucleic acid A, a nucleic acid A binding **probe** B, and one or more nucleic acid A binding **probes** C (See in particular Figures 1-4 and 10 and

page 14, last two lines to page 18, line 6 of the specification). The nucleic acid A binding **probe** B has a base sequence and a binding region that binds to the nucleic acid A (See *Id.*). The one or more nucleic acid binding **probes** C, in the aggregate, include a base sequence different from the base sequence on nucleic acid A binding **probe** B. (See *Id.*) The aggregate binding region of nucleic acid A binding **probe** C, which binds to the nucleic acid A, is longer as compared with the binding region of **probe** B (See *Id.*). The presence or amount of the triple stranded complexes may then be determined as an indication of the presence or amount of the nucleic acid A (See the specification at page 21, second paragraph and claims 31 and 82). Certain of the method claims (claims 37-40, 82-85) further require that exactly two nucleic acid A binding **probes** C are used to form the complex with the nucleic acid A and the nucleic acid A binding **probe** B. Certain other of the method claims (claims 48-52) further require that at least one of the nucleic acid A binding **probes** is a nucleic acid analog or a polymer comprised of a non-nucleotide monomer. Certain other of the method claims (claims 53 and 54) further require that either: 1) the triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A; or 2) the triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

In another embodiment, the invention is directed to triple stranded complexes

(claims 55-68) that can be used in the determination of nucleic acid and methods for forming the same (claims 69-81), wherein said complexes comprise the nucleic acid A and at least two separate and different probe molecules. In particular, the complex comprises a nucleic acid A, a nucleic acid A binding **probe** B and one or more nucleic acid A binding **probes** C (See Figures 1-4 and 10 and the specification at page 14, last two lines to page 18, line 6). Certain of the claimed complexes (claims 59-61) and methods of their preparation (claims 73-75) further require that exactly two nucleic acid A binding **probes** C are used to form the complex with the nucleic acid A and the nucleic acid A binding **probe** B. Certain other of the claimed complexes (claims 65-66) and methods of their preparation (claims 78 and 79) further require that at least one of the nucleic acid A binding **probes** is a nucleic acid analog. Certain other of the claimed complexes (claims 67-68) and methods of their preparation (claims 80-81) further require that either: 1) the triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A; or 2) the triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

## 6. ISSUES ON APPEAL

Claims 31-85 are pending in this application. No claim stands allowed.

Claims 31-85 were rejected under 35 U.S.C. § 112, first paragraph as containing new matter. Claims 31-85 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In addition, claims 31-85 were rejected under 35 U.S.C. §102(b) as being unpatentable over Svinarchuk et al. (J. Biol. Chem. 1995, Vol. 270(23), pages 14068-71).

Each of these grounds of rejections is respectfully traversed.

The issues on Appeal are whether or not the above-noted rejections are proper rejections under 35 U.S.C. §§ 112, first and second paragraphs and 35 U.S.C § 102(b).

## 7. GROUPING OF CLAIMS

It is stated that with respect to the rejections under 35 USC § 112, first and second paragraphs, all of the claims being rejected stand or fall together.

With respect to the rejection under 35 USC §102(b), it is respectfully stated that all of the claims being rejected do not stand or fall together. Appellants respectfully urge that the group (a) claims 31-36, 41-47, 55-58, 62-64, 69-72 and 76-77 should be considered with respect to whether the cited reference Svinarchuk et al. (*J. Biol. Chem., 270:* 14068-14071 (1995)) teaches a triple stranded complex which comprise a nucleic acid A and at least **two probes**.

Appellants respectfully urge that the group (b) claims 37-40, 59-61, 73-75 and 82-85 should be considered with respect to whether Svinarchuk et al. teaches a triple stranded complex comprising a nucleic acid A, a nucleic acid A binding probe B and additionally two nucleic acid binding **probes** C.

Appellants respectfully urge that the group (c) claims 48-52, 65-66 and 78-79 should be considered with respect to whether Svinarchuk et al. teaches a triple stranded complex comprising a probe that is a nucleic acid analog probe.

Finally, Appellants respectfully urge that group (d) claims 53-54, 67-68 and 80-81 should be considered with respect to whether Svinarchuk et al. teaches a triple stranded complex wherein either: 1) the triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A; or 2) the triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

## 8. APPELLANT'S ARGUMENTS

Appellants respectfully submit that claims 31-85 recite subject matter which is neither new matter, indefinite nor anticipated by the cited reference.

As noted above, the methods for determining nucleic acids via the formation of triple stranded binding complexes, the triple stranded binding complexes themselves

and the methods for producing said triple stranded binding complexes are under consideration. The Examiner has set forth three distinct rejections: claims 31-85 are rejected as: (1) containing new matter; (2) being indefinite; and (3) unpatentable over Svinarchuk et al.

1. Rejection of claims 31-85 as containing new matter

The Examiner asserts in Section 4 of the Office Action dated March 10, 2000 that the phrases "the aggregate" and "aggregate binding regions" recited in the claims constitute new matter. In particular, the Examiner asserts that the specification does not describe or discuss "aggregates" and that the description does not support "aggregate". The Examiner further asserts that the Stedman's dictionary definition of "aggregate" as "to unite or come together in a mass or cluster" sheds little light on such claim terms.

Appellants responded in a paper filed June 28, 2000, arguing that although the word "aggregate" does not appear in the application as filed, there is no requirement that words used in claims must exactly match those used in the specification (see MPEP §§ 2173(e) & 2163.07). Appellants urged that the law merely requires that the application reasonably convey to persons skilled in the art that, as of the filing date, the inventor had possession of the subject matter later claimed. *In re Edwards*, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978) and *Andco Environmental Processes Inc. v. Niagara Environmental Associates Inc.*, 224 U.S.P.Q. 43 (USDC, W.D. New York, 1984). Appellants further asserted that the term "aggregate" is generally used

to mean "more than one unit taken as a whole", "a whole sum or amount" or "considered as a whole" and that such language is clearly supported by the present application. In an Advisory Action dated July 20, 2000, the Examiner responded by arguing that "while the exact language is not required in the original specification, the meaning and use of aggregate in the claims has not been supported."

Appellants urge that the Examiner is simply incorrect. In establishing disclosure, the law is clear that the Applicant may rely on the original specification and claims as well as the original drawings as filed. *In re Lukach*, 442 F.2d 967, 58 CCPA 1233, 169 USPQ 795 (CCPA 1971); *In re Driscoll*, 562 f.2d 1245, 195 USPQ 434 (CCPA 1977); *In re Edwards*, 568 F.2d 1349, 196 USPQ 465 (CCPA 1978). Information contained in any one of the specification, claims or drawings of the application as filed may be added to any other part of the application without introducing new matter. MPEP § 2163.06 (III).

Appellants urge that the claimed invention is disclosed by the application as filed. The claimed invention is directed to triple stranded complexes which include one or more probes C which, in the aggregate, include a base sequence different from the base sequence of probe B. The one or more binding probes C, in the aggregate, also include an aggregate binding region which is longer as compared with the binding region of probe B. As asserted during prosecution of the present invention, the language "aggregate" and "aggregate binding region" indicates that there can be more than one probe C binding to nucleic acid A where probe B is

bound. In other words, at the location where probe B is bound to nucleic acid A, it is not required that one continuous strand of probe C binds to nucleic acid A. Instead, there can be several different probes C which bind to different regions of nucleic acid A at the same time.

Appellants point to the Webster's II: New Riverside University Dictionary 86 (1988) (see attached) definition of the term "aggregate" as "[a] total or whole considered with reference to its constituent parts." Appellants respectfully urge that such language is clearly supported by the present application which shows more than one probe C binding to nucleic acid A. Appellants point to Figures 3, 4 and 10 which discloses more than one probe C. Figures 3, 4 and 10 teach more than one probe C, in particular probes C1 and C2, having different sequences that bind to different regions of nucleic acid A at the same time.

Appellants also point to the specification at page 17, bottom paragraph to page 18, first paragraph which describes two probes C1 and C2 as indicated in both Figure 3 and 4. The specification at page 17, bottom paragraph teaches that where the two probes C1 and C2 are used, the two can act together to promote the binding of a probe B to the nucleic acid A. The specification at page 18, first paragraph also teaches that wherein two probes C1 and C2 are used, the overall length of the binding regions of C1 and C2 is larger than the binding region of probe B. In other words, the present application as filed makes it clear that "strand C" of the triple stranded complex may be composed of several parts or an "aggregate" (e.g., C1 and

C2). The present application also makes it clear that "aggregate binding region" refers to the binding regions of all probes C (e.g., C1 and C2), to be considered as a whole.

Because the forgoing remarks and comments conclusively demonstrate that the application, as filed, disclosed the use of two or more nucleic acid A binding probes C that acted, in the aggregate, to form the triple stranded structures disclosed in the specification, Appellants respectfully request withdrawal of the rejection.

2. Rejection of claims 31-85 as being indefinite

The Examiner asserts in Section 5 of the Office Action dated March 10, 2000 that the claims are indefinite because the phrase "in the aggregate" lacks antecedent basis. The Examiner also asserts that the claims are indefinite because it is unclear what is meant by the phrase "an aggregate binding region". In particular, the Examiner asserts that it is unclear whether the aggregate binding region is located on nucleic acid A or probe C and what physical and chemical features define the aggregate binding region.

In the response filed June 28, 2000, Appellants urged that the claims were not indefinite as alleged by the Examiner. Appellants urged that clearly those of skill in the art would understand the meaning of the phrases "aggregate" and "aggregate binding region" as used in the context of the claims as considered in light of the teachings of the application as filed. The Examiner responded in an Advisory Action

dated July 20, 2000, arguing that because Appellants suggested that an alternative definition explains the use of the term "aggregate" in the claims and since there are two possible definitions, the term "aggregate" is unclear.

Appellants urge that the Examiner is simply incorrect. A determination of indefiniteness is improper where claims define patentable subject matter with a reasonable degree of particularity and distinctiveness. MPEP § 2173.02 In determining whether or not the claims describe the invention with a reasonable degree of certainty, the language must be analyzed in light of the teachings of the prior art and the subject disclosure, as filed. MPEP § 2173.05(a) and *In re Moore*, 58 C.C.P.A. 1042, 439 F.2d 1232, 169 U.S.P.Q. 236 (CCPA, 1971) A claim term is definite where the scope of the term would be reasonably ascertainable by those skilled in the art when considering the art and the contents of the disclosure. *Id.*

As a preliminary matter, Appellants respectfully submit that the Examiner's statements contained in the Advisory Action dated July 20, 2000 constitute a fundamentally improper basis to sustain the rejection. The Examiner in effect argues that any term capable of having more than one meaning cannot be used in a claim. The Examiner in effect argues that if two or more meanings for a particular claim term exist, the claim will be *prima facia* indefinite in violation of the requirements of 35 USC § 112, second paragraph. It is respectfully submitted that there is no legal precedent for this interpretation of the statute. Instead, Appellants urge that in determining the meaning of a particular claim term, the term must be read in light of

the application, including the claims, specification and drawings, as filed. Because the Examiner has failed to offer any facts or evidence as to why the contents of the specification are insufficient to provide clarity of interpretation of the claims, but rather chose to rely on the fact that the term "aggregate" is capable of two or more definitions, it is respectfully submitted that the Examiner has failed to meet its proper legal burden for maintaining the rejection under 35 U.S.C. §112, second paragraph.

Nevertheless, Appellants urge that one skilled in the art viewing the application would know what it meant by the phrases "aggregate" and "aggregate binding region". Appellants point to the discussion above of the Webster's II definition of the term "aggregate" as well as Figures 3, 4 and 10 and the description at page 17, bottom paragraph to page 18, first paragraph of the specification. In light of such discussion, Appellants urge that one skilled in the art viewing the application would understand that the triple stranded complex may be composed of several probes C or an "aggregate" and that the phrase "aggregate binding region" refers to the binding regions of all probes C, taken together. Furthermore, the application makes it clear that the phrase "aggregate binding region" refers to probe C. The application, as filed, as well as claims 31-85 indicate a nucleic acid A and more than one probe C, and accordingly, the phrase "aggregate binding region" clearly applies to the binding region that is formed by the one or more binding probes C.

Regarding the physical and chemical features that define the aggregate binding region, one skilled in the art viewing the application, including Figures 3, 4

and 10, would conclude that the "aggregate binding region" is the base sequence of one or more binding probes C that bind with nucleic acid A and participate in forming the triple stranded complex with binding probe B in the instant claims. One skilled in the art would understand that a triple helix is formed from hydrogen bonding of nucleobase containing subunits of the component polymers and that the triple stranded complex is comprised of the component binding regions of each of the component polymers that hybridize and assemble to form the double and triple helix structures taught in the present application. Since there can be two or more binding probes C, it is clearly the aggregate binding region of the two or more probes C which together must bind to nucleic acid A and participate in the formation of the triple stranded complex of the present invention.

It is respectfully submitted that the forgoing remarks and arguments conclusively demonstrate that the application, as filed, contained information sufficient for the ordinary practitioner, at the time of the invention, to understand the meaning of "aggregate" and "aggregate binding region" as used in the presently appealed claims. Hence, Appellants respectfully request withdrawal of the present rejection under 35 USC § 112, second paragraph.

3. Rejection of claims 31-85 as being anticipated by Svinarchuk et al.

The Examiner asserts that the claims are anticipated by Svinarchuk et al. More specifically, the Examiner asserts in Section 6 of the Office Action dated March 10, 2000 that "Svinarchuk teaches triple helix formation wherein "the stability of

**double stranded DNA** is increased by the binding of the third strand" (abstract)". (emphasis added) The Examiner further asserts that "[a]s seen in Figure 3, there is only **one** nucleic acid binding probe C in the triple stranded region, nucleic acid binding probe B is smaller that nucleic acid binding probe C, nucleic acid binding probe C has a length of at least 6 [subunits], nucleic acid binding probe B is capable of having either an asymmetrical or a symmetrical base sequence, nucleic acid binding probe B is bound to nucleic acid A via Hoogsteen base pairing while nucleic acid binding probe C is bound to nucleic acid A via Watson Crick binding, and nucleic acid binding probe C fully spans the region of nucleic acid binding probe B". (emphasis added) The Examiner further states that "[i]t is noted that Svinarchuk teaches a double stranded molecule with **a probe** hybridized to a specific region" and that Svinarchuk teaches detection of the triplex formation. (emphasis added)

In the response filed on June 28, 2000, Appellants argued that Svinarchuk et al. does not disclose all of the elements of claims 31-85 and in particular, that Svinarchuk et al. **does not describe two binding probes**. It is noted with particularity that in the Advisory Action dated July 20, 2000, the Examiner did not offer any specific arguments in rebuttal to Applicant's response but nevertheless maintained the rejection under 35 U.S.C. § 102(b).

Appellants respectfully urge that the Examiner's determination of anticipation is simply incorrect. Any determination of anticipation requires that a reference disclose each and every elements of the claims. MPEP § 2131. The claimed

invention requires the use of at least **two probe molecules** (probe B and one or more of probes C) to form a triplex stranded complex that is then detected. In stark contrast, Appellants take the position that Svinarchuk et al. discloses a composition formed of a **single probe** molecule that binds to a double stranded nucleic acid plasmid to thereby form a triple helical structure and that this interpretation of Svinarchuk et al is entirely consistent with express statements made by the Examiner about this reference.

a) Group (a) claims 31-36, 41-47, 55-58, 62-64, 69-72 and 76-77

Appellants respectfully urge that group (a) claims 31-36, 41-47, 55-58, 62-64, 69-72 and 76-77 are not anticipated because the Svinarchuk et al. reference does not teach or suggest a triple stranded complex which comprises a nucleic acid A, and at least **two probes**. As a preliminary matter it is noted that the original claims 1-30 recited a nucleic acid binding **molecule** B and one or more a nucleic acid binding **molecules** C. However, each of the presently appealed claims require a nucleic acid binding **probe** B and one or more nucleic acid binding **probes** C. Hence, Appellants urge that an essential factor in establishing patentability for the group (a) claims is determining the meaning of the claim term **probe** and specifically whether Svinarchuk et al. teaches or suggests at least **two probes**.

Appellants respectfully submit that one of the Examiner's errors in maintaining this rejection clearly lies in a mischaracterization of a strand of the nucleic acid analyte to be determined in the assay described by Svinarchuk et al. as being a

**probe**. Appellants point to the Marion-Webster online dictionary (www.m-w.com) (see attached) which defines "probe" as:

> 1 : a slender medical instrument used especially for exploration (as of a would or bodily cavity); 2a : any of various testing devices or substances: as (1) : a pointed metal tip for making electrical contact with a circuit element being checked (2) : a usually small object that is inserted into something so as to test conditions at a given point (3) : a device used to penetrate or send back information especially from outer space or a celestial body (4) : **a device (as an ultrasound generator) or a substance (as DNA in genetic research) used to obtain specific information for diagnostic or experimental purposes** (emphasis added) b : a pipe on the receiving airplane thrust into the drogue of the delivering airplane in air refueling; 3a : the action of probing b : a penetrating or critical investigation c : a tentative exploratory advance or survey. (emphasis added)

Accordingly, not every nucleic acid molecule can be properly characterized as a probe and more importantly a probe is something that is used to interrogate or explore in order to obtain information about the object of the investigation, e.g. the target or as used in the subject specification - the analyte nucleic acid A (see page 5 of the specification, first two complete paragraphs). Therefore, a probe is not passive in that it is targeted for investigation nor is a probe a component of the molecule targeted for interrogation or investigation.

With this definition in mind, Appellants urge that the Examiner's error is most obvious when considered in light of the Examiner's own admission that Svinarchuk et al. teaches a double stranded molecule with **a probe** hybridized to a specific region. (See Office Action dated March 10, 2000, at the top of page 5) (emphasis

added) By the Examiner's own admission, there is **only one single probe molecule** operating to interrogate the double stranded plasmid. Even though at page 4 of the Office Action dated March 10, 2000 the Examiner characterizes one of the strands of the plasmid that is targeted (the analyte nucleic acid A) as being the nucleic acid A binding probe C, this is clearly error since the target of the investigation (i.e. the double stranded plasmid including its component strands) cannot, by definition, be a probe since it is the object of the investigation and not the investigating or interrogating molecule. The Examiner's description notwithstanding, there simply is not a **second probe** used to interrogate the double stranded plasmid nucleic acid analyte of Svinarchuk et al.

In stark contrast to the triple stranded complex of Svinarchuk et al, the claimed invention is directed to a triple stranded complex formed between a nucleic acid A, a nucleic acid A binding **probe** B and one or more nucleic acid A binding **probes** C for determining the amount of nucleic acid A. The claimed invention thus requires a triple stranded complex formed of **at least two nucleic acid binding probes** (probe B and one or more probes C) and a nucleic acid A. Because Svinarchuk et al. discloses only a complex comprising a single probe rather than two probes as required by claimed invention, Appellants respectfully urge that the rejection of group (a) claims 31-36, 41-47, 55-58, 62-64, 69-72 and 76-77 under 35 U.S.C. § 102(b) is improper and should be withdrawn.

b) Group (b) claims 37-40, 59-61, 73-75 and 82-85

Appellants respectfully urge that group (b) claims 37-40, 59-61, 73-75 and 82-85 are not anticipated because Svinarchuk et al. does not teach or suggest a triple stranded complex comprising a nucleic acid A, a nucleic acid A binding **probe** B and **two** nucleic acid binding **probes** C. As discussed above, Appellants urge that Svinarchuk et al. discloses only a **single probe** molecule, and therefore, cannot anticipate the group (b) claims. However, Appellants furthermore urge that the group (b) claims require the additional claim element of two nucleic acid binding **probes** C which is not taught or suggested by Svinarchuk et al.

As noted above, the Examiner states that "[a]s seen in Figure 3 [of Svinarchuk et al.], there is only **one** nucleic acid binding probe C in the triple stranded region..." (emphasis added) Appellants agree with this statement and urge, as discussed above, that Svinarchuk et al. discloses only a single probe molecule operating to interrogate a double stranded plasmid. However, the group (b) claims 37-40, 59-61, 73-75 and 82-85 all require that two nucleic acid binding **probes** C be used in either of: i) a method to determine the nucleic acid A; ii) a method to form the triple stranded complex; or iii) a triple stranded complex itself. Because Svinarchuk et al. clearly does not disclose, suggest or teach this additional claim element of claims 37-40, 59-61, 73-75 and 82-85, it is respectfully submitted that the rejection of these claims under 35 USC § 102(b) should properly be withdrawn.

c) Group (c) claims 48-52, 65-66 and 78-79

Appellants respectfully urge that group (c) claims 48-52, 65-66 and 78-79 are not anticipated because Svinarchuk et al. does not teach or suggest a triple stranded complex comprising a probe that is a nucleic acid analog probe. In particular, Appellants respectfully urge that the group (c) claims require the additional claim element of a nucleic acid analog probe which is not taught or suggested by Svinarchuk et al. Appellants also note that as discussed above, Svinarchuk et al. discloses only a **single probe** molecule, and therefore, cannot anticipate the group (c) claims.

Although the Examiner alleges that Svinarchuk et al. anticipates the group (c) claims, Appellants urge that the Examiner has provided no evidence that Svinarchuk et al. teaches or suggests a triple stranded complex comprising probes that are nucleic acid analogs. Indeed, Appellants respectfully submit that Svinarchuk et al. does not, in fact, teach or suggest a triple stranded complex comprising any probe that is a nucleic acid analog. It is also respectfully submitted that each of the group (c) claims requires that the triple stranded complex described in said claims each requires that at least one probe be a nucleic acid analog. In the absence of any evidence in the record that would indicate that the triple stranded complexes of Svinarchuk et al. teach the limitation of a probe that is a nucleic acid analog, it is respectfully submitted that it is clear error to reject group (c) claims 48-52, 65-66 and 78-79 under 35 U.S.C. § 102(b). Hence, withdrawal of the rejection is requested.

d) Group (d) claims 53-54, 67-68 and 80-81

Appellants urge that the group (d) claims 53-54, 67-68 and 80-81 are also not anticipated by Svinarchuk et al. Appellants urge that the group (d) claims are not anticipated because, as discussed above, Svinarchuk et al. discloses only a **single probe** molecule. However, Appellants also urge that Svinarchuk et al. does not teach or suggest the additional group (d) claim element of either: 1) the triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A; or 2) the triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

Although the Examiner asserts that Svinarchuk et al. teach that "the stability of **double stranded DNA** is increased by the binding of the third strand" (abstract)", this is not the equivalent of the specific elements of the group (d) claims. (emphasis added) Indeed, Appellants urge that Svinarchuk et al. does not teach or suggest these additional claim elements of the group (d) claims. In the absence of any evidence in the record that would indicate that Svinarchuk et al. does teach such additional claim elements, it is respectfully submitted that it is clear error to reject the group (d) claims 53-54, 67-68 and 80-81 under 35 U.S.C. § 102(b). Appellants thus respectfully request withdrawal of the rejection.

For all of the above noted reasons, it is strongly contended that claims 31-85

do not contain new matter. It is also strongly contended that claims 31-85 are not indefinite. It is further most strongly contended that certain clear differences exist between the present invention as claimed in claims 31-85, in particular the group (a), (b), (c) and (d) claims, and the Svinarchuk et al. reference relied upon by the Examiner.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of claims 31-85.

In the event that this paper is not being timely filed, Appellant respectfully petitions for an appropriate extension of time. Any fees for such an extension together with any additional fees which may be due with respect to this paper may be charged to Counsel's Deposit Account 01-2300.

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Encls: Appendix (claims on appeal)
Appendix Webster's II: New Riverside University Dictionary 86 (1988)
Marion-Webster online dictionary (www.m-w.com)

## 9. APPENDIX

Claims on Appeal

31. A method for determining the presence or amount of a nucleic acid A, comprising: (a) forming a triple stranded complex between said nucleic acid A, a nucleic acid A binding probe B, said nucleic acid A binding probe B having a base sequence and a binding region which binds to nucleic acid A, and one or more nucleic acid A binding probes C, wherein said one or more nucleic acid A binding probes C, in the aggregate, comprise a base sequence different from the base sequence of nucleic acid A binding probe B and an aggregate binding region wherein said aggregate binding region, which binds to nucleic acid A, is longer as compared with the binding region of probe B; and (b) determining the presence or amount of said triple stranded complex as an indication of the presence or amount of nucleic acid A.

32. The method according to claim 31 wherein said triple stranded complex contains only one nucleic acid A binding probe C.

33. The method according to claim 31 wherein said nucleic acid A binding probe B comprises a binding region of 4 to 10 bases.

34. The method according to claim 31 wherein said binding region of nucleic acid A binding probe B has an asymmetric base sequence.

35. The method according to claim 31 wherein said binding region of nucleic acid A binding probe B has a symmetric base sequence.

36. The method according to claim 31 wherein said aggregate binding region of the one or more nucleic acid A binding probes C has a length of at least 6 bases.

37. The method according to claim 31 wherein said triple stranded complex comprises two different nucleic acid A binding probes C which bind to different regions of nucleic acid A in the triple stranded region.

38. The method according to claim 37 wherein said two different nucleic acid A binding probes C of the triple stranded complex form an aggregate binding region which is comprised of two distinct triple helical binding regions, wherein each distinct triple helical binding region is formed from the binding of the two different probes C each to a distinct, non-overlapping, region on nucleic acid A.

39. The method according to claim 38 wherein said two different nucleic acid A binding probes C bind juxtaposed on nucleic acid A.

40. The method according to claim 38 wherein said triple stranded complex is at least six bases in length and each of the two different nucleic acid A binding probes C individually contribute at least one but less than eleven bases to said triple stranded complex.

41. The method according to claim 31 wherein said binding region of nucleic acid A binding probe B comprises only pyrimidine bases but the aggregate binding region of the one or more nucleic acid A binding probes C comprises at least one non-pyrimidine base.

42. The method according to claim 31 wherein said nucleic acid A binding probe B is bound to nucleic acid A via Hoogsteen base pairing and the one or more nucleic acid A binding probes C are bound to nucleic acid A via Watson Crick base pairing.

43. The method according to claim 31 wherein at least one of said nucleic acid A binding probes is labeled and the presence of said label in the triple stranded complex is used for determining the presence or amount of the nucleic acid A.

44. The method according to claim 32 wherein at least one of said nucleic acid A binding probes has been chemically modified to destabilize triple helix formation occurring by either of: (a) two nucleic acid A binding probes B binding to one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

45. The method according to claim 31 wherein a first nucleic acid not to be determined is differentiated from said nucleic acid A by a difference in the base sequence located outside the binding region of the nucleic acid A binding probe B but within the aggregate binding region of the one or more nucleic acid A binding probes C.

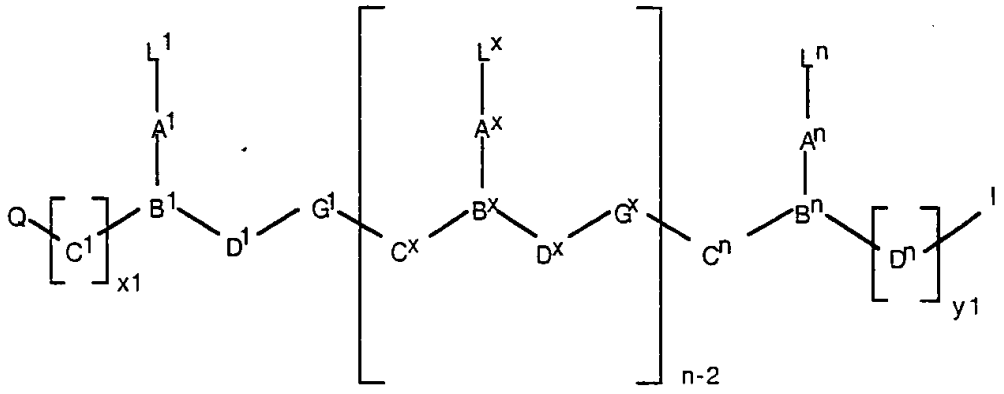
46. The method according to claim 31 wherein a first nucleic acid not to be determined is differentiated from said nucleic acid A by a difference in the base sequence located within the binding region of the nucleic acid A binding probe B.

47. The method according to claim 31 wherein a reaction mixture is used for forming the triple stranded complex, said reaction mixture containing a competitive probe D which can compete with at least one nucleic acid A binding probe C in binding to nucleic acid A, but which is incapable of participating in the formation of the triple stranded complex.

48. The method according to claim 31 wherein at least one of said nucleic acid A binding probes is a nucleic acid analogue.

49. The method according to claim 48 wherein said nucleic acid analogue is a peptide nucleic acid.

50. The method according to claim 31 wherein at least one of said nucleic acid A binding probes is a polymer of the general Formula I



Formula I

wherein

n is an integer of from at least 3,

x is an integer of from 2 to n-1,

each of $L^1$-$L^n$ is a ligand independently selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_4$)alkanoyl, naturally occurring nucleobases, non-naturally occurring nucleobases, aromatic moieties, DNA intercalators, nucleobase-binding groups, heterocyclic moieties, reporter ligands and chelating moieties, wherein at least one of $L^1$ -$L^n$, preferably at least one of $L^2$-$L^{n-1}$ is a non-nucleobase electron acceptor or a

donor moiety and at least 2 of $L^1$-$L^n$ being a nucleobase binding group, or a naturally or non-naturally occurring nucleobase;

each of $C^1$-$C^n$ is $(CR^6R^7)_y$ (preferably $CR^6R^7$, $CHR^6CHR^7$ or $CR^6R^7CH_2$) where $R^6$ is hydrogen and $R^7$ is selected from the group consisting of the side chains of naturally occurring alpha amino acids, or $R^6$ and $R^7$ are independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, aryl, aralkyl, heteroaryl, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $NR^3R^4$ and $SR^5$, where $R^3$ and $R^4$ are as defined below, and $R^5$ is hydrogen, $(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, or $(C_1$-$C_6)$alkylthio-substituted $(C_1$-$C_6)$alkyl or $R^6$ and $R^7$ taken together complete an alicyclic or heterocyclic system; or $C^1$-$C^n$ is CO, CS, $CNR^3$;

each of $D^1$-$D^n$ is $(CR^6R^7)_z$ (preferably $CR^6R^7$, $CHR^6CHR^7$ or $CH_2CR^6R^7$) where $R^6$ and $R^7$ are as defined above;

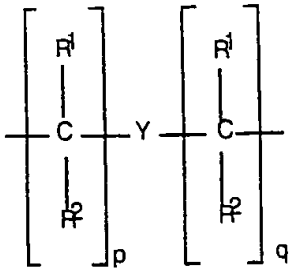
each of y and z is zero or an integer from 1 to 10, the sum y + z being at least 2, preferably greater than 2, but not more than 10;

each of $G^1$-$G^{n-1}$ is $-NR^3CO-$, $-NR^3CS-$, $-NR^3SO-$ or $-NR^3SO^{2-}$, in either orientation, where $R^3$ is as defined below;

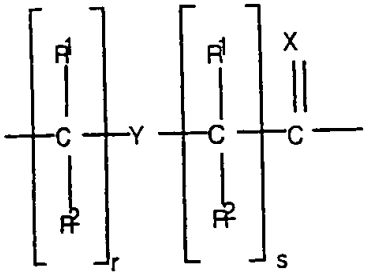
each of $A^1$-$A^n$ and $B^1$-$B^n$ are selected such that:

(a) $A^1$-$A^n$ is a group of formula (I/A), (I/B), (I/C) or (I/D), and $B^1$-$B^n$ is N or $R^3N+$; or

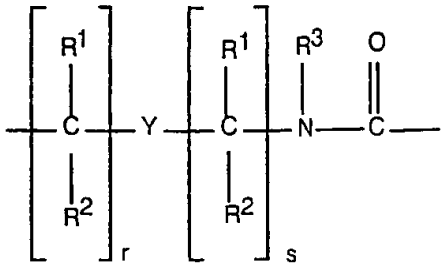
(b) $A^1$-$A^n$ is a group of formula (I/D) and $B^1$-$B^n$ is CH;



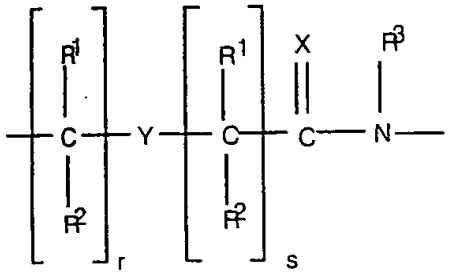
Formula I/A



Formula I/B



Formula I/C



Formula I/D

wherein:

X is O, S, Se, $NR^3$, $CH_2$ or $C(CH_3)_2$;

Y is a single bond, O, S or $NR^4$;

each of p and q is zero or an integer from 1 to 5, (the sum p+q being preferably not more than 5);

each of r and s is zero or an integer from 1 to 5, (the sum r+s being preferably not more than 5);

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, ($C_1$-$C_4$)alkyl which may be hydroxy- or ($C_1$-$C_4$)alkoxy- or ($C_1$-$C_4$)alkylthio-substituted, hydroxy, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkylthio, amino and halogen; and

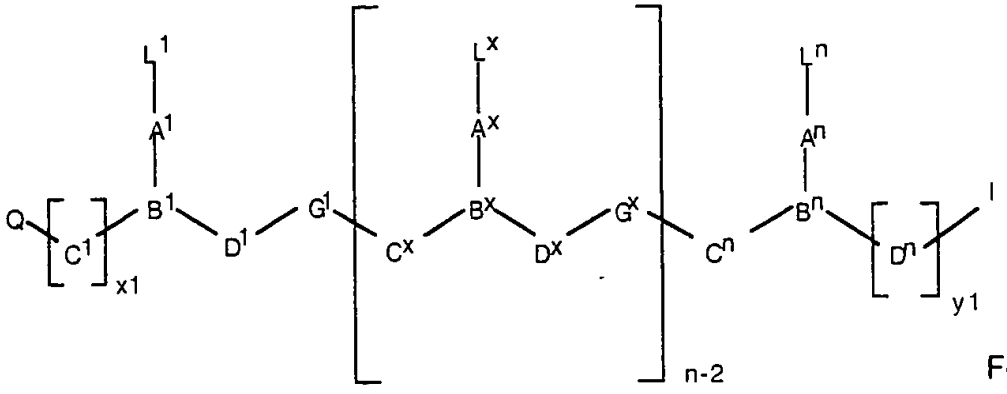
each $R^3$ and $R^4$ is independently selected from the group consisting of hydrogen, ($C_1$-$C_4$)alkyl, hydroxy- or alkoxy- or alkylthio-substituted ($C_1$-$C_4$)alkyl, hydroxy, ($C_1$-$C_6$)-alkoxy, ($C_1$-$C_6$)-alkylthio and amino;

Q and I is independently selected from -$CO_2H$, -CONR'R", -$SO_3H$ or -$SO_2$NR'R" or an activated derivative of -$CO_2H$ or -$SO_3H$ and -NR'R"'

where R', R" and R"' are independently selected from the group consisting of hydrogen, alkyl, amino protecting groups, reporter ligands, intercalators, chelators, peptides, proteins, carbohydrates, lipids, steroids, nucleosides, nucleotides, nucleotide diphosphates, nucleotide triphosphates, oligonucleotides, including both oligoribonucleotides and oligodeoxyribonucleotides, oligonucleosides and soluble and non-soluble polymers and as well as nucleic acid binding moieties and

each of x1 and y1 is an integer of from 0 to 10.

51. A method according to claim 31 wherein at least one of said nucleic acid A binding probes is a polymer of the general Formula I



Formula I

wherein

n is an integer of from at least 3,

x is an integer of from 2 to n-1,

each of $L^1$-$L^n$ is a ligand independently selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_4$)alkanoyl, naturally occurring nucleobases, non-naturally occurring nucleobases, aromatic moieties, DNA intercalators, nucleobase-binding groups, heterocyclic moieties, reporter ligands and chelating moieties, wherein at least one of $L^1$-$L^n$, preferably at least one of $L^2$-$L^{n-1}$ is a non-nucleobase electron acceptor or a donor moiety and at least 2 of $L^1$-$L^n$ being a nucleobase binding group, or a naturally or non-naturally occurring nucleobase;

each of $C^1$-$C^n$ is $(CR^6R^7)_y$ (preferably $CR^6R^7$, $CHR^6CHR^7$ or $CR^6R^7CH_2$) where $R^6$ is hydrogen and $R^7$ is selected from the group consisting of the side chains of naturally occurring alpha amino acids, or $R^6$ and $R^7$ are independently selected from the group consisting of hydrogen, ($C_1$-$C_6$)alkyl, aryl, aralkyl, heteroaryl, hydroxy, ($C_1$-$C_6$)alkoxy, ($C_1$-$C_6$)alkylthio, $NR^3R^4$ and $SR^5$, where $R^3$ and $R^4$ are as defined below, and $R^5$ is hydrogen, ($C_1$-$C_6$)alkyl, hydroxy, ($C_1$-$C_6$)alkoxy, or ($C_1$-$C_6$)alkylthio-substituted ($C_1$-$C_6$)alkyl or $R^6$ and $R^7$ taken together complete an alicyclic or heterocyclic system; or $C^1$-$C^n$ is CO, CS, $CNR^3$;

each of $D^1$-$D^n$ is $(CR^6R^7)_z$ (preferably $CR^6R^7$, $CHR^6CHR^7$ or $CH_2CR^6R^7$) where $R^6$ and $R^7$ are as defined above;

each of y and z is zero or an integer from 1 to 10, the sum y + z being at least 2, preferably greater than 2, but not more than 10;

each of $G^1$-$G^{n-1}$ is $-NR^3CO-$, $-NR^3CS-$, $-NR^3SO-$ or $-NR^3SO^{2-}$, in either orientation, where $R^3$ is as defined below;

each of $A^1$-$A^n$ and $B^1$-$B^n$ are selected from (Ia), (Ib) or (Ic) such that:

(Ia): $B^1$-$B^n$ is N and $A^1$-$A^n$ is $-CO-(CH_2)_6-$

(Ib): $B^1$-$B^n$ is N and $A^1$-$A^n$ is $-CO-NR^3-(CH_2)_2-$

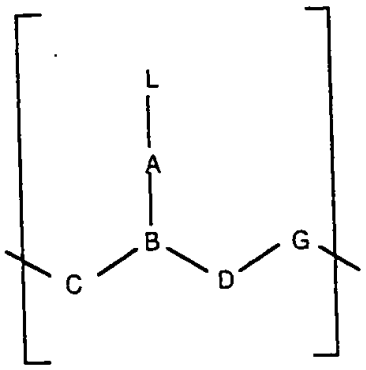
(Ic): $B^1$-$B^n$ is CH and $A^1$-$A^n$ is $-NR^3-CO-(CH_2)_2-$

Q and I is independently selected from $-CO_2H$, -CONR'R", $-SO_3H$ or $-SO_2NR'R"$ or an activated derivative of $-CO_2H$ or $-SO_3H$ and -NR'R"'

where R', R" and R"' are independently selected from the group consisting of hydrogen, alkyl, amino protecting groups, reporter ligands, intercalators, chelators, peptides, proteins, carbohydrates, lipids, steroids, nucleosides, nucleotides, nucleotide diphosphates, nucleotide triphosphates, oligonucleotides, including both oligoribonucleotides and oligodeoxyribonucleotides, oligonucleosides and soluble and non-soluble polymers and as well as nucleic acid binding moieties and

each of x1 and y1 is an integer of from 0 to 10.

52. The method according to claim 31 wherein at least one of said nucleic acid A binding probes comprise at least one monomer subunit of general Formula III




Formula III

each of L is a ligand independently selected from the group consisting of hydrogen, hydroxy, $C_1$-$C_4$)alkanoyl, naturally occurring nucleobases, non-naturally occurring nucleobases, aromatic moieties, DNA intercalators, nucleobase-binding groups, heterocyclic moieties, reporter ligands and chelating moieties, wherein at least one of L is a non-nucleobase electron acceptor or a donor moiety and at least 2 of L being a nucleobase binding group, or a naturally or non-naturally occurring nucleobase;

each of C is $(CR^6R^7)_y$ where $R^6$ is hydrogen and $R^7$ is selected from the group consisting of the side chains of naturally occurring alpha amino acids, or $R^6$ and $R^7$ are independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, aryl, aralkyl, heteroaryl, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $NR^3R^4$ and $SR^5$, where $R^3$ and $R^4$ are as defined below, and $R^5$ is hydrogen, $(C_1$-$C_6)$alkyl, hydroxy, $(C_1$-$C_6)$alkoxy, or $(C_1$-$C_6)$alkylthio-substituted $(C_1$-$C_6)$alkyl or $R^6$ and $R^7$ taken together complete an alicyclic or heterocyclic system; or C is CO, CS, $CNR^3$;

each of D is $(CR^6R^7)_z$ where $R^6$ and $R^7$ are as defined above;

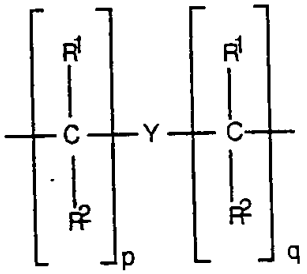
each of y and z is zero or an integer from 1 to 10, the sum y + z being at least 2;

each of G is $-NR^3CO-$, $-NR^3CS-$, $-NR^3SO-$ or $-NR^3SO^{2-}$, in either orientation, where $R^3$ is as defined below;

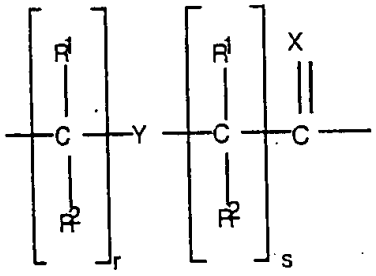
each of A and B are selected such that:

(a) A is a group of formula (I/A), (I/B), (I/C) or (I/D), and B is N or $R^3N+$; or

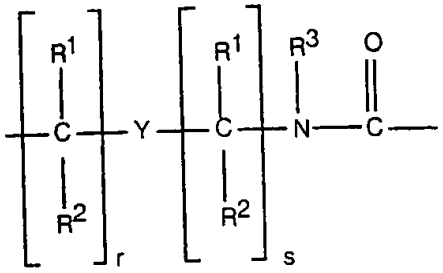
(b) A is a group of formula (I/D) and B is CH;



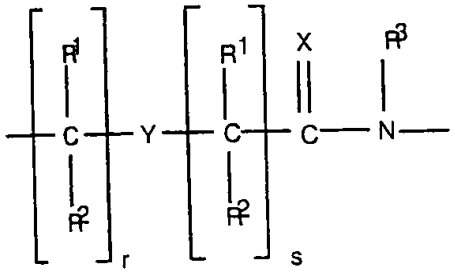
Formula I/A



Formula I/B



Formula I/C



Formula I/D

wherein:

X is O, S, Se, $NR^3$, $CH_2$ or $C(CH_3)_2$; Y is a single bond, O, S or $NR^4$;

each of p and q is zero or an integer from 1 to 5,

each of r and s is zero or an integer from 1 to 5,

each $R^1$ and $R^2$ is independently selected from the group consisting of hydrogen, ($C_1$-$C_4$)alkyl which may be hydroxy- or ($C_1$-$C_4$)alkoxy- or ($C_1$-$C_4$)alkylthio-substituted, hydroxy, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)alkylthio, amino and halogen; and

each $R^3$ and $R^4$ is independently selected from the group consisting of hydrogen, ($C_1$-$C_4$)alkyl, hydroxy- or alkoxy- or alkylthio-substituted ($C_1$-$C_4$)alkyl, hydroxy, ($C_1$-$C_6$)-alkoxy, ($C_1$-$C_6$)-alkylthio and amino;

where R', R" and R"' are independently selected from the group consisting of hydrogen, alkyl, amino protecting groups, reporter ligands, intercalators, chelators, peptides, proteins, carbohydrates, lipids, steroids, nucleosides, nucleotides, nucleotide diphosphates, nucleotide triphosphates, oligonucleotides, including both oligoribonucleotides and oligodeoxyribonucleotides, oligonucleosides and soluble and non-soluble polymers and as well as nucleic acid binding moieties and

each of x1 and y1 is an integer of from 0 to 10.

53. The method according to claim 31 wherein said triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A.

54. The method according to claim 32 wherein said triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

55. A triple stranded complex comprising a nucleic acid A, a nucleic acid A binding probe B, said nucleic acid A binding probe B having a base sequence and a binding region which binds to nucleic acid A, and one or more nucleic acid A binding probes C wherein said one or more nucleic acid A binding probes C, in the aggregate, comprise a base sequence different from the sequence of nucleic acid A binding probe B and an aggregate binding region wherein said aggregate binding region, which binds to nucleic acid A, is longer as compared with the binding region of nucleic acid A binding probe B.

56. The complex according to claim 55 containing only one nucleic acid A binding probe C.

57. The complex according to claim 55 wherein said nucleic acid A binding probe B comprises a binding region of 4 to 10 bases.

58. The complex according to claim 55 wherein said aggregate binding region of the one or more nucleic acid A binding probes C has a length of at least 6 bases.

59. The complex according to claim 55 wherein said triple stranded complex comprises two different nucleic acid A binding probes C.

60. The complex according to claim 59 wherein said two different nucleic acid A binding probes C of the triple stranded complex form an aggregate binding region which is comprised of two distinct triple helical binding regions, wherein each distinct triple helical binding region is formed from the binding of the two different nucleic acid A binding probes C each to a distinct, non-overlapping, region on nucleic acid A.

61. The complex according to claim 60 wherein said two different nucleic acid A binding probes C bind juxtaposed on nucleic acid A.

62. The complex according to claim 55 wherein said binding region of nucleic acid A binding probe B comprises only pyrimidine bases but the aggregate binding region of the one or more nucleic acid A binding probes C comprises at least one non-pyrimidine base.

63. The complex according to claim 55 wherein said nucleic acid A binding probe B is bound to nucleic acid A via Hoogsteen base pairing and the one or more nucleic acid A binding probes C are bound to nucleic acid A via Watson Crick base pairing.

64. The complex according to claim 55 wherein at least one of said nucleic acid A binding probes is labelled and the presence of said label in the triple stranded complex is used for determining the presence or amount of the nucleic acid A.

65. The complex according to claim 55 wherein at least one of said nucleic acid A binding probes is a nucleic acid analogue.

66. The complex according to claim 55 wherein said nucleic acid analogue is a peptide nucleic acid.

67. The complex according to claim 55 wherein said triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A.

68. The complex according to claim 56 wherein said triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

69. A method of forming a triple stranded binding complex comprising reacting a nucleic acid molecule A with a nucleic acid A binding probe B, said nucleic acid A binding probe B having a base sequence and binding region which binds to nucleic acid A, and one or more nucleic acid A binding probes C, wherein said one or more nucleic acid A binding probes C, in the aggregate, comprise a base sequence different from the sequence of nucleic acid A binding probe B and an aggregate binding region wherein said aggregate binding region, which binds to nucleic acid A, is longer as compared with the binding region of nucleic acid A binding probe B.

70. The method according to claim 69 wherein said triple stranded complex contains only one nucleic acid A binding probe C.

71. The method according to claim 69 wherein said nucleic acid A binding probe B comprises a binding region of 4 to 10 bases.

72. The method according to claim 69 wherein said aggregate binding region of the one or more nucleic acid A binding probes C has a length of at least 6 bases.

73. The method according to claim 69 wherein said triple stranded complex comprises two different nucleic acid A binding probes C.

74. The method according to claim 69 wherein said two different nucleic acid A binding probes C of the triple stranded complex form an aggregate binding region which is comprised of two distinct triple helical binding regions, wherein each distinct triple helical binding region is formed from the binding of the two different nucleic acid A binding probes C each to a distinct, non-overlapping, region on nucleic acid A.

75. The method according to claim 74 wherein said two different nucleic acid A binding probes C bind juxtaposed on nucleic acid A.

76. The method according to claim 69 wherein said binding region of nucleic acid A binding probe B comprises only pyrimidine bases but the aggregate binding region of

the one or more nucleic acid A binding probes C comprises at least one non-pyrimidine base.

77. The method according to claim 69 wherein said nucleic acid A binding probe B is bound to nucleic acid A via Hoogsteen base pairing and the one or more nucleic acid A binding probes C are bound to nucleic acid A via Watson Crick base pairing.

78. The method according to claim 69 wherein at least one of said nucleic acid A binding probes is a nucleic acid analogue.

79. The method according to claim 69 wherein said nucleic acid analogue is a peptide nucleic acid.

80. The method according to claim 69 wherein said triple stranded complex is more thermostable than a triple stranded complex formed by two nucleic acid A binding probes B binding with one nucleic acid A.

81. The method according to claim 70 wherein said triple stranded complex is more thermostable than a triple stranded complex formed from either of: (a) two nucleic acid A binding probes B binding with one nucleic acid A; or (b) two of said nucleic acid A binding probes C binding with one nucleic acid A.

82. A method for determining the presence or amount of a nucleic acid A, comprising: (a) forming a triple stranded complex between said nucleic acid A, a nucleic acid A binding probe B, said nucleic acid A binding probe B having a base

sequence and a binding region which binds to nucleic acid A, and two nucleic acid A binding probes C, wherein said two nucleic acid A binding probes C, in the aggregate, comprise a base sequence different from the base sequence of nucleic acid A binding probe B and an aggregate binding region wherein said aggregate binding region, which binds to nucleic acid A, is longer as compared with the binding region of nucleic acid A binding probe B; and (b) determining the presence or amount of said nucleic acid A by measuring for the presence or amount of said triple stranded complex.

83. The method according to claim 82 wherein said two nucleic acid A binding probes C of the triple stranded complex are different and form an aggregate binding region which is comprised of two distinct triple helical binding regions, wherein each distinct triple helical binding region is formed from the binding of the two different nucleic acid A binding probes C each to a distinct, non-overlapping, region on nucleic acid A.

84. The method according to claim 83 wherein said two different nucleic acid A binding probes C bind juxtaposed on nucleic acid A.

85. The method according to claim 83 wherein said triple stranded complex is at least six bases in length and each of the two different nucleic acid A binding probes C individually contribute at least one but less than eleven bases to said triple stranded complex.

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**ag·gran·dize** (ə-grăn'dīz', ăg'rən-) *vt.* **-dized, -diz·ing, -diz·es.** [Fr. *aggrandir, aggrandiss-* : *a-*, to (< Lat. *ad-*) + *grandir*, to grow larger < Lat. *grandire* < *grandis*, large.] **1.** To increase the scope of : EXTEND. **2.** To make greater in power, influence, or reputation. **3.** To exaggerate the qualities of : EXALT. **—ag·gran'dize·ment** (ə-grăn'dīz-mənt, -dīz'-) *n.* **—ag·gran'diz'er** *n.*

**ag·gra·vate** (ăg'rə-vāt') *vt.* **-vat·ed, -vat·ing, -vates.** [Lat. *aggravare, aggravat-* : *ad*, to + *gravare*, to burden < *gravis*, heavy.] **1.** To make worse <bronchitis *aggravated* by smoking> **2.** *Informal.* To annoy <a talkative student who *aggravated* the teacher> **—ag'gra·vat'ing·ly** *adv.* **—ag'gra·va'tive** *adj.* **—ag'gra·va'tor** *n.*

**aggravated assault** *n. Law.* Any of various assaults that are more serious than a common assault, esp. one performed with intent to commit a crime.

**ag·gra·va·tion** (ăg'rə-vā'shən) *n.* **1.** The act of aggravating or state of being aggravated. **2.** One that irritates or makes worse. **3.** *Informal.* Annoyance : vexation.

**ag·gre·gate** (ăg'rĭ-gĭt) *adj.* [ME *aggregat* < Lat. *aggregare*, to add to : *ad-*, to + *gregare*, to collect < *grex*, flock.] **1.** Gathered together into a mass constituting a whole. **2.** *Bot.* Crowded or massed into a dense cluster. **3.** Composed of a mixture of minerals separable by mechanical means. —*n.* (-gĭt). **1.** A total or whole considered with reference to its constituent parts <an empire that was the *aggregate* of many states> **2.** The mineral materials, as sand or stone, used in making concrete. —*vt.* (-gāt') **-gat·ed, -gat·ing, -gates.** **1.** To gather into a mass, sum, or whole. **2.** To amount to. **—ag'gre·gate·ly** *adv.* **—ag'gre·ga'tion** *n.* **—ag'gre·ga'tive** *adj.* **—ag'gre·ga'tor** *n.*

**aggregate fruit** *n.* A fruit, as the raspberry, developed from the pistils of a single flower and consisting of a mass of drupelets.

**aggregate fruit**
*Two types of aggregate fruit:* (left) *a raspberry and* (right) *a strawberry*

**ag·gress** (ə-grĕs') *vi.* **-gressed, -gress·ing, -gress·es.** [Fr. *aggresser* < Lat. *aggredi* : *ad-*, toward + *gradi*, to go.] To commit aggression.

**ag·gres·sion** (ə-grĕsh'ən) *n.* **1.** Initiation of forceful, usu. hostile action against another : ATTACK. **2.** The practice of attacking or encroaching, esp. in violation of territorial rights : INVASION. **3.** *Psychoanal.* Hostile action or behavior.

**ag·gres·sive** (ə-grĕs'ĭv) *adj.* **1.** Hostile : combative. **2. a.** Energetic and enterprising. **b.** Boldly assertive. **—ag·gres'sive·ly** *adv.* **—ag·gres'sive·ness** *n.*

**ag·gres·sor** (ə-grĕs'ər) *n.* One that engages in aggression.

**ag·grieve** (ə-grēv') *vt.* **-grieved, -griev·ing, -grieves.** [ME *agreven* < OFr. *agrever* < Lat. *aggravare*, to make worse. —see AGGRAVATE.] **1.** To distress or afflict. **2.** To injure unjustly.

**ag·grieved** (ə-grēvd') *adj.* **1.** Feeling distress or affliction. **2.** Treated wrongly : OFFENDED. **3.** *Law.* Treated unjustly, as by a decision of a court. **—ag·griev'ed·ly** (ə-grē'vĭd-lē) *adv.* **—ag·griev'ed·ness** *n.*

**a·gha** (ä'gə, äg'ə) *n. var. of* AGA.

**a·ghast** (ə-găst') *adj.* [ME *agast*, p.part. of *agasten*, to frighten : *a-* (intensive) + *gasten*, to frighten < OE *gæstan* < *gāst*, ghost.] Stricken with horror : APPALLED.

**ag·ile** (ăj'əl, ăj'īl') *adj.* [OFr. < Lat. *agilis* < *agere*, to impel.] **1.** Able to move quickly and easily : NIMBLE. **2.** Mentally alert. **—ag'ile·ly** *adv.* **—ag'ile·ness** *n.* **—a·gil'i·ty** (ə-jĭl'ĭ-tē) *n.*

**†a·gin** (ə-gĭn') *prep. Regional.* Against..

**ag·ing** (ā'jĭng) *n.* **1.** The process of becoming old or mature. **2.** An artificial process for imparting the characteristics and properties of age, as to wood.

**ag·i·o** (ăj'ē-ō') *n., pl.* **-os.** [Ital. < Med. Gk. *allagion*, exchange < *allagé*, change < *allos*, other.] **1.** A premium paid for exchanging one currency for another. **2.** An allowance or premium for the difference in value between two currencies being exchanged.

**ag·i·tate** (ăj'ĭ-tāt') *v.* **-tat·ed, -tat·ing, -tates.** [Lat. *agitare, agitat-*, freq. of *agere*, to impel.] —*vt.* **1.** To move with sudden forcefulness or violence <a hurricane *agitating* the trees> **2.** To upset emotionally. **3.** To try to arouse public interest in (e.g., a cause). **4.** *Archaic.* To ponder over. —*vi.* To stir up public interest in a cause. **—ag'i·tat'ed·ly** (-tā'tĭd-lē) *adv.* **—ag'i·ta'tive** *adj.*

**ag·i·ta·tion** (ăj'ĭ-tā'shən) *n.* **1. a.** The act of agitating. **b.** The state of being agitated. **2.** Extreme emotional disturbance : PERTURBATION. **3.** Arousal of public interest in a cause or controversial matter. **—ag'i·ta'tion·al** *adj.*

**ag·i·ta·to** (ăj'ĭ-tä'tō) *adj.* [Ital. < Lat. *agitare*, to agitate.] *Mus.* Fast and restless : AGITATED. —Used as a direction. **—ag'i·ta'to** *adv.*

**ag·i·ta·tor** (ăj'ĭ-tā'tər) *n.* **1.** One who agitates, esp. one who engages in political agitation. **2.** A mechanism that shakes or stirs, as in a washing machine.

**ag·it·prop** (ăj'ĭt-prōp') *n.* [R., department of agitation and propaganda : *agitatsiya*, agitation + *propaganda*, propaganda.] Communist-oriented political propaganda disseminated esp. through literature, drama, art, or music.

**A·gla·ia** (ə-glā'ə, ə-glī'ə) *n.* [Gk. < *aglaia*, splendor < *aglaos*, bright.] *Gk. Myth.* One of the Three Graces.

**a·gleam** (ə-glēm') *adj. & adv.* Shining brightly : GLEAMING.

**ag·let** (ăg'lĭt) *n.* [ME < OFr. *aguillette*, dim. of *aguille*, needle < LLat. *acicula*, dim. of Lat. *acus*, needle.] **1.** A tag or metal sheath on the end of a lace, cord, or ribbon to facilitate its passing through eyelet holes. **2.** An ornamental device similar to the aglet.

**a·gley** (ə-glī', ə-glā', ə-glē') *adv.* [Scottish : *a-*, on + *gley*, to squint < ME *glien.*] *Scot.* Awry : amiss.

**a·glim·mer** (ə-glĭm'ər) *adj. & adv.* Glimmering faintly.

**a·glit·ter** (ə-glĭt'ər) *adj.* Glittering : sparkling. **—a·glit'ter** *adv.*

**a·glow** (ə-glō') *adj. & adv.* Glowing.

**a·gly·con** (ə-glī'kŏn) *or* **a·gly·cone** (-kōn') *n.* A nonsugar component of a glycoside that is resolvable through hydrolysis.

**ag·mi·nate** (ăg'mə-nĭt, -nāt') *also* **ag·mi·nat·ed** (-nā'tĭd) *adj.* [< Lat. *agmen, agmin-*, multitude.] *Bot.* Gathered in clusters.

**ag·nail** (ăg'nāl') *n.* [ME *angnail*, corn < OE *angnægel*, a sore under the nail : *ang-*, tight + *nægel*, nail.] **1.** A hangnail. **2.** A painful swelling or sore around a fingernail or toenail.

**ag·nate** (ăg'nāt') *adj.* [Lat. *agnatus*, a relation on the father's side < p.part. of *agnasci*, to be born in addition to : *ad-*, to + *nasci*, to be born.] **1.** Related on or descended from the male or father's side. **2.** From a common source : AKIN. —*n.* A relative on the male or father's side only. **—ag·nat'ic** (ăg-nāt'ĭk) *adj.* **—ag·nat'i·cal·ly** *adv.* **—ag·na'tion** *n.*

**Ag·ni** (ŭg'nē) *n.* [Skt. *agniḥ*, fire.] The Vedic god of fire and guardian of humans.

**ag·no·men** (ăg-nō'mən) *n., pl.* **-nom·i·na** (-nŏm'ə-nə) [Lat. : *ad-*, to + *nomen*, name.] **1.** An additional cognomen given to a Roman citizen, often in honor of military victories. **2.** A nickname.

**ag·no·sia** (ăg-nō'zhə) *n.* [NLat. < Gk. *agnōsia*, ignorance : *a-*, not + *gnōsis*, knowledge < *gignōskein*, to know.] Pathologic loss of auditory, sensory, or visual comprehension.

**ag·nos·tic** (ăg-nŏs'tĭk) *n.* [< Gk. *agnōstos*, unknown : *a-*, not + *gnōstos*, known < *gignōskein*, to know.] One who believes that there can be no proof of the existence of God but does not deny the possibility that God exists. **—ag·nos'tic** *adj.* **—ag·nos'ti·cal·ly** *adv.*

**ag·nos·ti·cism** (ăg-nŏs'tĭ-sĭz'əm) *n.* **1.** *Philos.* The doctrines of the agnostics, holding that certainty or first or absolute truths are unattainable and that only perceptual phenomena are objects of exact knowledge. **2.** A theological theory that does not deny God but denies the possibility of knowing Him.

**Ag·nus De·i** (ăg'nəs dē'ī', än'yŏos dā'ē, äg'nōos') *n.* [Lat.] **1.** The Lamb of God, an emblem of Christ. **2.** An iconographic representation of the Agnus Dei. **3.** A liturgical prayer to Christ.

**a·go** (ə-gō') *adj. & adv.* [ME, p.part. of *agon*, to go away < OE *āgān* : *ā-* (intensive) + *gān*, to go.] Earlier than the present time : PAST <three months *ago*><died long *ago*>

**a·gog** (ə-gŏg') *adv. & adj.* [ME *agogge* < OFr. *en gogue*, in merriment.] In a state of excitement and keen anticipation.

**-agog** *suff. var. of* -AGOGUE.

**à go-go** *also* **à·go-go** (ə-gō-gō') *adv.* [Fr., galore. ] In a fast and lively manner : ENERGETICALLY.

**-agogue** *or* **-agog** *suff.* [LLat. *-agogus* < Gk. *-agogos* < *agein*, to lead.] A substance that stimulates the flow of <*hemagogue*>

**a·gone** (ə-gŏn', ə-gōn') *adj. & adv.* [ME *agon*, p.part. of *agon*, to go away. —see AGO.] *Archaic.* Gone by : PAST.

**a·gon·ic** (ā-gŏn'ĭk, ə-gŏn'-) *adj.* [< Gk. *agōnos* : *a-*, not + *gōnia*, angle.] Having no angle.

**agonic line** *n.* An imaginary line on the earth's surface connecting points where the magnetic declination is zero.

**ag·o·nist** (ăg'ə-nĭst) *n.* [Back-formation < ANTAGONIST.] **1.** *Physiol.* A muscle that contracts and is opposed by contraction in another muscle, the antagonist. **2.** One involved in a struggle or competition.

**ag·o·nis·tic** (ăg'ə-nĭs'tĭk) *also* **ag·o·nis·ti·cal** (-tĭ-kəl) *adj.* [Gk. *agōnistikos* < *agōnistēs*, combatant < *agōn*, contest.] **1.** Argumentative : combative. **2.** Struggling to achieve effect. **3.** Of or relating to athletic competitions, orig. those of the ancient Greeks. **—ag'o·nis'ti·cal·ly** *adv.*

**ag·o·nize** (ăg'ə-nīz') *v.* **-nized, -niz·ing, -niz·es.** [OFr. *agoniser* < Med. Lat. *agonizare* < Gk. *agōnizesthai*, to struggle < *agōn*, contest.] —*vi.* **1.** To be in extreme physical or emotional pain : suffer intensely. **2.** To make a great effort : STRUGGLE. —*vt.* To cause great pain or anguish to. **—ag'o·niz'ing·ly** *adv.*

**ag·o·ny** (ăg'ə-nē) *n., pl.* **-nies.** [ME *agonie* < OFr. < Med. Lat. *agonia* < Gk. *agōnia* < *agōn*, struggle.] **1.** The suffering of intense phys-

# Merriam-Webster's COLLEGIATE® DICTIONARY



Main Entry: **[1]probe**
Pronunciation: 'prOb
Function: *noun*
Etymology: Medieval Latin *proba* examination, from Latin *probare*
Date: 1580
**1** : a slender medical instrument used especially for exploration (as of a wound or bodily cavity)
**2 a** : any of various testing devices or substances: as (1) : a pointed metal tip for making electrical contact with a circuit element being checked (2) : a usually small object that is inserted into something so as to test conditions at a given point (3) : a device used to penetrate or send back information especially from outer space or a celestial body (4) : a device (as an ultrasound generator) or a substance (as DNA in genetic research) used to obtain specific information for diagnostic or experimental purposes **b** : a pipe on the receiving airplane thrust into the drogue of the delivering airplane in air refueling
**3 a** : the action of probing **b** : a penetrating or critical investigation **c** : a tentative exploratory advance or survey



\&\ as a and u in abut
\ᵊ\ as e in kitten
\&r\ as ur/er in further
\a\ as a in ash
\A\ as a in ace
\ä\ as o in mop
\au\ as ou in out
\ch\ as ch in chin
\e\ as e in bet
\E\ as ea in easy
\g\ as g in go
\i\ as i in hit
\I\ as i in ice
\j\ as j in job
\ŋ\ as ng in sing
\O\ as o in go
\o\ as aw in law
\oi\ as oy in boy
\th\ as th in thin
\th\ as th in the
\ü\ as oo in loot
\u\ as oo in foot
\y\ as y in yet
\zh\ as si in vision

* generally or often considered vulgar

|| usage restricted; consult a dictionary for more information

For more information see the Guide To Pronunciation and the Thesaurus Symbol Guide.